## REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1-13, 16-18, and 27-36 are pending in this application and are presented for examination. Claims 14-15, 19-26, and 29-30 have been canceled without prejudice. Claims 1-13 and 16-18 have been withdrawn from consideration as being directed to non-elected inventions. Claims 27 and 31 have been amended. Support is found, for example, on page 3, line 12 to page 4, line 16; page 17, lines 11-24; and in Table 1 on pages 93-100. As such, no new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

## I. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 27-36 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient written description. To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

### A. Inflammatory bowel diseases (IBDs)

In making this aspect of the rejection, the Examiner alleges that the specification and/or claims do not provide adequate written description to show possession of the entire genus of IBDs (*see,* Office Action at page 5). The Examiner contends that it is unclear whether the nucleic acid probes for the different genes can be used to monitor gene expression in all IBDs or in one type of IBD (*see, id*). In response, Applicant asserts that the specification clearly demonstrates to one of skill in the art that the present inventor was in full possession of the claimed invention at the time of filing.

As an initial matter, Applicant respectfully points out that, contrary to the Examiner's allegation, IBD does not encompass a variety of diseases with different symptoms and clinical manifestations. Rather, there are two major IBD subtypes, Crohn's disease (CD) and ulcerative colitis (UC), which share similar demographic and epidemiological features with as much as 10% of the cases being clinically indistinguishable (*see, e.g.,* the specification at page 1, lines 27-30). In fact, the Robbins *et al.* reference cited by the Examiner states that "there are many similarities between ulcerative colitis and Crohn's disease, and indeed there is a growing

tendency to consider them as a single entity - 'inflammatory bowel diseases (IBD).' Not only do these two diseases have many overlapping features, but the belief grows ever stronger that they represent variable tissue or immunologic responses to a common, albeit still unknown, etiologic agent" (*see,* Robbins *et al.*, Pathologic Basis of Disease, 2nd Ed. (1979) at page 982, right column). As such, a subject diagnosed as having either CD or UC also has IBD.

Applicant asserts that the instant specification adequately describes how the nucleic acid probes for the different genes can be used to monitor gene expression in the two major IBD subtypes, *i.e.,* CD and UC. In particular, the specification at pages 12-17 and 93-100 (Table 1) provides numerous examples of genes that are differently expressed in CD and/or UC relative to control samples. Because CD and UC are subtypes of IBD, a difference in the expression level of any of the genes listed in Table 1 compared to an expression level of the same gene in healthy tissue would indicate that a subject has IBD or is at risk of developing IBD, irrespective of whether that gene is differentially expressed in CD or UC. Thus, a diagnosis of IBD does not depend on which of the two major IBD subtypes differentially expresses that gene.

For example, the presently claimed array, which comprises nucleic acid probes for determining the expression level of at least three genes selected from the group consisting of GRO3, HNL, elafin, and COL6A3, can be used to determine whether a subject has IBD or is at risk of developing IBD. In particular, Table 1 shows that GRO3, HNL, and COL6A3 are overexpressed in UC samples relative to healthy tissue, and elafin is overexpressed by almost 4-fold in UC samples relative to CD samples. Because UC is a subtype of IBD, a difference in the expression level of at least three of the claimed genes compared to healthy tissue would indicate that a subject has IBD or is at risk of developing IBD. Therefore, a diagnosis of IBD can be made using the presently claimed array.

In view of the foregoing remarks, the disclosure of the instant specification is more than adequate to demonstrate to one of skill in the art that Applicant had possession of the presently claimed genus of IBDs at the time the application was filed. Accordingly, Applicant respectfully requests withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

B. Nucleic acid probes

In making this aspect of the rejection, the Examiner alleges that one of skill in the art would not be able to envision the specific sequences of the nucleic acid probes on the claimed array (*see,* Office Action at page 6). In response, Applicant asserts that the specification clearly demonstrates to one of skill in the art that the present inventor was in full possession of the claimed invention at the time of filing.

As set forth in MPEP § 2163(II)(A)(3)(a), an adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). For biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. *See,* MPEP § 2163(II)(A)(3)(a).

Contrary to the Examiner's allegation, the disclosure of numerous identifying characteristics for the nucleic acid probes in the instant specification is more than sufficient to demonstrate to one of skill in the art that Applicant was in possession of the invention as claimed. First, the specification provides the structure and length of the nucleic acid probes used in the claimed array. In particular, the specification sets forth that a nucleic acid probe is typically an oligonucleotide comprising a sequence of at least about 12-40 nucleotides in length which is complementary to a portion of the coding sequence of a claimed gene (*see, e.g.,* page 82, lines 17-30). Nucleic acid probes such as oligonucleotides can be synthesized by standard methods known in the art using, for example, an automated DNA synthesizer (*see, e.g.,* page 58, lines 22-31).

Second, the specification provides the binding specificity of the nucleic acid probes used in the claimed array. For example, the specification sets forth that a nucleic acid probe is typically an oligonucleotide comprising a sequence which hybridizes under stringent conditions to a portion of the coding sequence of a claimed gene (*see, e.g.,* page 6, lines 21 to page 7, line 2). Hybridization conditions of low, medium, or high stringency are described, for example, on page 35, line 13 to page 36, line 14 of the instant specification. Additionally, the

specification discloses that a nucleic acid probe can specifically hybridize to a portion of the coding sequence of a claimed gene, such that it has less than 15% background hybridization to a nucleic acid encoding a different protein (*see, e.g.,* page 31, lines 10-21). In particular, an oligonucleotide probe specifically hybridizes to a portion of the coding sequence of a claimed gene when it detects only the specific gene and does not hybridize to similar or related nucleic acids (*see, e.g.,* page 31, lines 21-24).

Third, the specification provides the sequence of the nucleic acid probes used in the claimed array. As an initial matter, Applicant asserts that Table 1 provides the nucleotide sequence of each of the claimed genes, which is obtained by entering its GenBank accession number into the National Center for Biotechnology Information (NCBI) online database (http://www.ncbi.nlm.nih.gov/). The Examiner alleges that because the GenBank sequence of a claimed gene may be updated and revised at any time, the sequence of a claimed gene could change at any time (*see,* Office Action at page 6). However, one of skill in the art can easily determine the nucleotide sequence of each of the claimed genes at the time of filing by entering its GenBank accession number into the NCBI "Sequence Revision History" website (http://www.ncbi.nlm.nih.gov/entrez/sutils/girevhist.cgi) and selecting a version of the GenBank sequence which corresponds to the sequence known in the art at that time. For the Examiner's convenience, Applicant has enclosed a copy of the nucleotide sequence of each of the claimed genes as of the filing date of the instant application.

Based on the identifying characteristics described above, one of skill in the art would recognize that the sequence of a nucleic acid probe corresponds to the complement of a portion of the coding sequence of a claimed gene which is at least about 12-40 nucleotides in length and hybridizes under stringent conditions to that portion of the coding sequence. To identify stretches of non-homologous coding sequence in the claimed gene, the specification discloses that the coding sequence can be processed using an alignment algorithm or program such as BLAST or FASTA (*see, e.g.,* page 25, line 6 to page 27, line 8). Nucleic acid probes having a sequence complementary to a portion of the non-homologous coding sequence can then be designed and bound to a suitable substrate (*see, e.g.,* page 6, line 21 to page 7, line 2).

In view of the foregoing remarks, the disclosure of the instant specification is more than adequate to demonstrate to one of skill in the art that Applicant had possession of the presently claimed nucleic acid probes at the time of the application was filed. Accordingly, Applicant respectfully requests withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

## II. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 27-36 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

In the Office Action, the Examiner alleges that it is unclear which subject the term "said subject" is referring to in claim 27 (*see,* Office Action at page 7). The Examiner also alleges that the phrase "expression level of said gene product differs by at least a factor of two" is not clearly defined in claim 31 (*see, id*).

In order to expedite prosecution of the present case, Applicant has amended claim 27 to recite that a difference in the expression level of each of the genes determined in the subject compared to an expression level of the same gene in healthy tissue indicates that the subject has IBD or is at risk of developing IBD. Similarly, Applicant has amended claim 31 to recite that the expression level of each of the genes determined in the subject differs from the expression level of the same gene in healthy tissue by at least a factor of two. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

## III. REJECTION UNDER 35 U.S.C. § 102(e)

Claims 27-36 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Cocks *et al.* (U.S. Patent No. 6,607,879). To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

For a rejection of claims under § 102 to be properly founded, the Examiner must establish that a single prior art reference either expressly or inherently discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231

USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

In the Office Action, the Examiner alleges that Cocks *et al.* teaches a microarray comprising cDNAs including GRO-gamma (*i.e.,* GRO3) for diagnosing an immunopathological condition such as CD or UC by comparing the hybridization patterns from diseased and non-diseased samples (*see,* Office Action at pages 8-9). In response, Applicant asserts that Cocks *et al.* fails to teach all of the elements of the claimed invention.

In order to expedite prosecution of the present case, Applicant has amended claim 27 to recite an array comprising nucleic acid probes for determining the expression level of at least three genes selected from the group consisting of GRO3, HNL, elafin, and COL6A3. Applicant asserts that Cocks *et al.* discloses detecting the altered expression of GRO3 using a cDNA microarray for diagnosing an immunopathological condition such as CD or UC, but fails to teach or suggest the presently claimed array in which the expression level of at least three of the claimed genes are determined. In fact, Cocks *et al.* does not teach or suggest determining the expression level of HNL, elafin, or COL6A3. As a result, Cocks *et al.* does not anticipate the presently claimed array because each and every element as set forth in amended claim 27 is not found in the reference. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection under 35 U.S.C. § 102(e).

## IV. REJECTION UNDER 35 U.S.C. § 103(a)

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations. MPEP § 2143. *See also, In re Rouffet,* 47 USPQ2d 1453. The court in *Rouffet* stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (1999).

A. Dieckgraefe *et al.* in view of Nielsen *et al.*

Claims 27-36 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dieckgraefe *et al.* (*Gastroenterology*, 114:A964-965 (1998)) in view of Nielsen *et al.* (*Gut*, 38:414-420 (1996)). To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

In the Office Action, the Examiner alleges that it would have been *prima facie* obvious for one of skill in the art to generate an array with nucleic acid probes that specifically hybridize to NGAL (*i.e.,* HNL) for the purpose of diagnosing IBD based on the combined teaching of Dieckgraefe *et al.* and Nielsen *et al.* (*see,* Office Action at page 11). In response, Applicant asserts that the combination of references fails to teach all of the elements of the claimed invention. Moreover, one of skill in the art would not be motivated to combine the references.

As discussed above, Applicant has amended claim 27 to recite an array comprising nucleic acid probes for determining the expression level of at least three genes selected from the group consisting of GRO3, HNL, elafin, and COL6A3. Applicant asserts that Dieckgraefe *et al.* discloses an oligonucleotide probe array that detected changes in the expression of different classes of genes in IBD specimens, but without reference to any particular genes in those classes. As a result, Dieckgraefe *et al.* fails to teach or suggest the presently claimed array in which the expression level of at least three of the claimed genes are determined.

In fact, the Examiner has acknowledged that Dieckgraefe *et al.* does not specifically teach any of the claimed genes (*see,* Office Action at page 10).

Nielsen *et al.* does not supply the teaching that is clearly lacking in Dieckgraefe *et al.* Specifically, Nielsen *et al.* discloses strong HNL expression in the colonic epithelium of CD and UC specimens, but fails to teach or suggest the presently claimed array in which the expression level of at least three of the claimed genes are determined. As a result, given the absence of any teaching or suggestion in these references that at least three of the claimed genes are differentially expressed in IBD relative to control samples, none of these references, either alone or in combination, would read on the presently claimed array. In addition, one of skill in the art would not have been motivated to include at least three of the claimed genes on an array for diagnosing IBD because it was not appreciated that their detection would lead to an improved diagnosis of IBD based on the information provided by these references.

In view of the foregoing, the combined disclosures of Dieckgraefe *et al.* and Nielsen *et al.* do not render the presently claimed array obvious. Accordingly, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

B. Dieckgraefe *et al.* in view of Cocks *et al.*

Claims 27-36 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dieckgraefe *et al.* (*Gastroenterology*, 114:A964-965 (1998)) in view of Cocks *et al.* To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

In the Office Action, the Examiner alleges that it would have been *prima facie* obvious for one of skill in the art to generate an array with nucleic acid probes that specifically hybridize to GRO3 for the purpose of diagnosing IBD based on the combined teaching of Dieckgraefe *et al.* and Cocks *et al.* (*see,* Office Action at page 12). In response, Applicant asserts that the combination of references fails to teach all of the elements of the claimed invention. Moreover, one of skill in the art would not be motivated to combine the references.

As discussed above, Applicant has amended claim 27 to recite an array comprising nucleic acid probes for determining the expression level of at least three genes selected from the group consisting of GRO3, HNL, elafin, and COL6A3. Applicant asserts that

Dieckgraefe *et al.* discloses an oligonucleotide probe array that detected changes in the expression of different classes of genes in IBD specimens, but without reference to any particular genes in those classes. As a result, Dieckgraefe *et al.* fails to teach or suggest the presently claimed array in which the expression level of at least three of the claimed genes are determined. Again, the Examiner has acknowledged that Dieckgraefe *et al.* does not specifically teach any of the claimed genes (*see,* Office Action at page 12).

Cocks *et al.* does not supply the teaching that is clearly lacking in Dieckgraefe *et al.* Specifically, Cocks *et al.* discloses detecting the altered expression of GRO3 using a cDNA microarray for diagnosing an immunopathological condition such as CD or UC, but fails to teach or suggest the presently claimed array in which the expression level of at least three of the claimed genes are determined. As a result, given the absence of any teaching or suggestion in these references that at least three of the claimed genes are differentially expressed in IBD relative to control samples, none of these references, either alone or in combination, would read on the presently claimed array. In addition, one of skill in the art would not have been motivated to include at least three of the claimed genes on an array for diagnosing IBD because it was not appreciated that their detection would lead to an improved diagnosis of IBD based on the information provided by these references.

As such, the combined disclosures of Dieckgraefe *et al.* and Cocks *et al.* do not render the presently claimed array obvious. Accordingly, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

C. Heller *et al.* in view of Cocks *et al.*

Claims 27-36 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Heller *et al.* (*Proc. Natl. Acad. Sci. USA*, 94:2150-2155 (1997)) in view of Cocks *et al.* To the extent the rejection applies to the amended claims, Applicant respectfully traverses the rejection.

In the Office Action, the Examiner alleges that it would have been *prima facie* obvious for one of skill in the art to generate an array with nucleic acid probes that specifically hybridize to GRO3 for the purpose of diagnosing IBD based on the combined teaching of Heller

*et al.* and Cocks *et al.* (*see,* Office Action at page 14). In response, Applicant asserts that the combination of references fails to teach all of the elements of the claimed invention. Moreover, one of skill in the art would not be motivated to combine the references.

As discussed above, Applicant has amended claim 27 to recite an array comprising nucleic acid probes for determining the expression level of at least three genes selected from the group consisting of GRO3, HNL, elafin, and COL6A3. Applicant asserts that Heller *et al.* discloses the differential expression of genes from rheumatoid arthritis and IBD samples that do not correspond to any of the claimed genes. In fact, the Examiner has acknowledged that Heller *et al.* does not specifically teach any of the claimed genes (*see,* Office Action at page 14).

Cocks *et al.* does not supply the teaching that is clearly lacking in Heller *et al.* Again, Cocks *et al.* discloses detecting the altered expression of GRO3 using a cDNA microarray for diagnosing an immunopathological condition such as CD or UC, but fails to teach or suggest the presently claimed array in which the expression level of at least three of the claimed genes are determined. As a result, given the absence of any teaching or suggestion in these references that at least three of the claimed genes are differentially expressed in IBD relative to control samples, none of these references, either alone or in combination, would read on the presently claimed array. In addition, one of skill in the art would not have been motivated to include at least three of the claimed genes on an array for diagnosing IBD because it was not appreciated that their detection would lead to an improved diagnosis of IBD based on the information provided by these references.

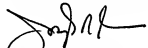
Therefore, the combined disclosures of Heller *et al.* and Cocks *et al.* do not render the presently claimed array obvious. Accordingly, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

## CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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Aug 15 2006 13:27:38

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  TITLE     Cloning and expression of human neutrophil lipocalin cDNA derived
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  AUTHORS   Sallenave,J.M. and Silva,A.
  TITLE     Characterization and gene sequence of the precursor of elafin, an
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  JOURNAL   Am. J. Respir. Cell Mol. Biol. 8 (4), 439-445 (1993)
   PUBMED   8476637
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Comment Features Sequence

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  AUTHORS   Chu,M.L., Zhang,R.Z., Pan,T.C., Stokes,D., Conway,D., Kuo,H.J.,
            Glanville,R., Mayer,U., Mann,K., Deutzmann,R. and Timpl,R.
  TITLE     Mosaic structure of globular domains in the human type VI collagen
            alpha 3 chain: similarity to von Willebrand factor, fibronectin,
            actin, salivary proteins and aprotinin type protease inhibitors
  JOURNAL   EMBO J. 9 (2), 385-393 (1990)
   PUBMED   1689238
REFERENCE   2  (bases 1 to 10558)
  AUTHORS   Chu,M.L.
  TITLE     Direct Submission
  JOURNAL   Submitted (18-SEP-1997) Chu, M.L. Thomas Jefferson University, Dept
            of Biochemistry & Molec Biology, 233 South 10th Street,
            Philadelphia, PA 19107, USA
  REMARK    revised by author 30-SEP-97 and [3]
REFERENCE   3  (bases 1 to 10558)
  AUTHORS   Chu,M.L.
  TITLE     Direct Submission
  JOURNAL   Submitted (08-MAY-1998) Chu, M.L. Thomas Jefferson University, Dept
            of Biochemistry & Molec Biology, 233 South 10th Street,
            Philadelphia, PA 19107, USA
COMMENT     On May 12, 1998 this sequence version replaced gi:2462471.
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